

THE CHARACTERS
OF
OFFICIAL IRON ARSENATE

BY
FREDERICK B. POWER, PH.D.
AND
HAROLD ROGERSON, M.Sc.



THE WELLCOME CHEMICAL RESEARCH LABORATORIES
FREDERICK B. POWER, PH.D., *Director*
6, King Street, Snow Hill
LONDON, E.C.

THE CHARACTERS OF OFFICIAL IRON ARSENATE.*

BY

FREDERICK B. POWER & HAROLD ROGERSON.

The compound described in the British Pharmacopœia of 1898 under the title of *Ferri Arsenas* (Iron Arsenate) is defined by the same authority as "ferrous arsenate, $\text{Fe}_3(\text{AsO}_4)_2, 6\text{H}_2\text{O}$, with ferric arsenate and some iron oxide."

It is apparent from the above statement that the article is recognised as a mixture, and, with consideration of the method of preparation and the change which it is known to undergo on keeping, it must necessarily show considerable variation in composition. The definition of the official compound would, however, lead one to assume that the iron is chiefly in the ferrous state, which is not the case, and there would also appear to be no justification for assuming, as is indicated, that the ferrous arsenate contained in this amorphous compound is represented by the definite formula $\text{Fe}_3(\text{AsO}_4)_2, 6\text{H}_2\text{O}$. The introduction of this formula may perhaps be attributable to the fact that a ferrous arsenate occurs in nature in the form of the mineral symplectite, which has been considered to have the above composition ('Handbuch der anorganischen Chemie,' by O. Dammer, 1893, Bd. III., p. 352), although, according to Groth ('Tabellarische Uebersicht der Mineralien,' second edition, 1882, p. 67), it contains eight molecules of water, and is isomorphous with vivianite, $\text{Fe}_3(\text{PO}_4)_2, 8\text{H}_2\text{O}$. It is possible, however, that the formula in question, which is also referred to in the Pharmacopœia in connection with the determination of the amount

* A contribution from the Welleome Chemical Research Laboratories, London, to the British Pharmaceutival Conference, Aberdeen, September, 1908, and reprinted from *The Pharmaceutical Journal*, September 19, 1908.

of hydrous ferrous arsenate in the official compound, is merely a reproduction of a very old statement occurring in Wittstein's 'Vierteljahresschrift für Pharm.,' 15, 185, and quoted in Graham-Otto's 'Lehrbuch der anorganischen Chemie,' fifth edition, pt. 4, p. 600. In the latter work, for example, it is noted that "by double decomposition between sodium arsenate and ferrous sulphate a white precipitate of the composition $\text{Fe}''_3(\text{AsO}_4)_2 \cdot 6\text{H}_2\text{O}$ is produced, together with an acid salt which remains in solution," in accordance with the following equation :—



A similar statement is recorded in Gmelin's 'Handbook of Chemistry,' vol. V., p. 305, on the authority of Chenevix, whose analyses, however, are not at all in agreement with the formula proposed for the compound. Inasmuch as there is no evidence nor the least probability that the hydrous ferrous arsenate in the official preparation contains any definite or uniform amount of water, the adoption of a formula which would lead to such a conclusion appears to be both inconsistent and completely devoid of significance.¹

As a test for the quality of iron arsenate, the Pharmacopœia directs that, besides giving "no characteristic reaction with the tests for sulphates," it should contain such an amount of ferrous salt as will correspond to at least "nearly 12½ per cent. of hydrous, or 10 per cent. of anhydrous ferrous arsenate." Various commentators have previously called attention to the fact that this requirement is not an altogether satisfactory one, inasmuch as iron arsenate is chiefly of value therapeutically on account of its arsenic content, yet the ferrous iron alone is estimated, while the arsenic is not. (Compare *Pharm. Journ.*, 1898, 61, p. 530; 1900, 65, p. 150; *Chemist and Druggist*, May, 1900, p. 884; 'Year-Book of Pharmacy,' 1900, p. 334; also the 'United States Dispensatory,' eighteenth edition, p. 605.)

In reply to these observations the Editor of the Pharmacopœia has given the following motive for the test.² "The

¹ An analogous and equally inconsistent statement occurs in the Pharmacopœia under *Ferri Phosphas* (Iron Phosphate), which is defined as "a powder containing not less than 47 per cent. of hydrous ferrous phosphate, $\text{Fe}_3(\text{PO}_4)_2 \cdot 8\text{H}_2\text{O}$, with ferric phosphate and some iron oxide." In this case the formula is evidently deduced from that of the crystallised mineral vivianite.

² 'Report for 1898, on the Progress of Pharmacy in its Relation to the Future Revision of the Pharmacopœia of 1898: a Digest of Researches and Criticisms.' By Dr. John Attfield, F.R.S. London 1900.

ferrous iron is estimated as a means of determining the condition of the salt. If no ferrous salt other than arsenate were present the official volumetric test would indirectly show the proportion of arsenium. Conversion of the ferrous arsenate into magnesium pyroarsenate, weighing the latter, would show whether or not this is the case, and thus either confirm the trustworthiness of the official procedure, as regards arsenium as well as iron—that is, ferrous arsenate, as officially contemplated—or displace a process of inferior by one of superior usefulness.”

This exposition of the official test does not appear to afford very convincing evidence of its value, and is not altogether logical, for, with consideration of the character of iron arsenate, it is evident that a determination of the amount of ferrous iron alone can give no indication, either directly or indirectly of the proportion of arsenic present in the compound. It is of interest to note in this connection that in Attfield's 'Manual of Chemistry,' seventeenth edition, 1898, p. 778, this fact is recognised by the statement that “the compound is more nearly a ferric than a ferrous arsenate.”

An attempt has been made to ascertain the period at which iron arsenate was first introduced as a medicinal agent, and from the following record it would appear to have been employed as early as 1809. Pereira, for example, in his 'Elements of Materia Medica and Therapeutics,' fourth edition, 1854, vol. 1, p. 856, states that arseniate of iron is “obtained by adding the arseniate of potash, soda, or of ammonia to a solution of protosulphate of iron,” and has noted, with the subjoined reference, that “Mr. Carmichael used it externally in ulcerated cancer” (Carmichael: 'Essay on the Effects of Carbonate and other Preparations of Iron upon Cancer,' pp. 50, 66, 341, 343, *et seq.*, 1809).

The 'Pharmacopée Universelle,' par A. J. L. Jourdan, tome premier-Paris, 1828, p. 216, refers to the salt as follows: “*Arséniate de Fer. Aucune pharmacopée n'indique la manière de préparer ce sel.*” It gives, however, a formula for the preparation of “*Pilules d'Arséniate de Fer,*” which appears to have been taken from the following work: Ratier (F.S.), 'Formulaire pratique des hôpitaux civils de Paris,' third edition, Paris, 1827. The above-mentioned pills contained one-sixteenth of a grain each of iron arsenate, and the following indications were given for their use:—“*Conseillées, d'après les Anglais, dans les affections cancéreuses et les dartres ulcérées. Dose, une pilule par jour.*” A method

for preparing the salt was given in 'L'Officine,' par Dorvault, pharmacien, Paris, 1844, p. 154, as follows: "*Arséniate de Fer.—S'obtient en décomposant une solution de sulfate de fer, par une autre d'arséniate de potasse; on recueille et on lave le précipité, qui est de l'arséniate de fer.*"

Iron arsenate was not included in the last editions of the London (1851), Edinburgh (1841), and Dublin (1850) Pharmacopœias, and its first official recognition therefore appears to have been in the British Pharmacopœia of 1864. Although the article was retained in all the subsequent revisions of the latter work, a comparison of the text clearly indicates that the subject has always been one of considerable perplexity to those who were entrusted with the compilation of the Pharmacopœia, as well as to those who were expected to be guided by it. The divergencies with respect to the method of preparation and the requirements embodied in the quantitative tests are, in fact, quite remarkable, as may be seen by the following abstracts from the successive editions of the British Pharmacopœia.

In the Pharmacopœia of 1864 *Ferri Arsenias* was defined as "Arseniate of Iron, $3\text{FeO}, \text{AsO}_5$, partially oxidated." It was prepared by the interaction of ferrous sulphate (9 parts) and sodium arseniate, dried at 300°F . (4 parts), with sodium acetate (3 parts); the latter salt having been used to obviate any loss which otherwise would have been occasioned by the solvent action of free sulphuric acid. The solution of the compound in hydrochloric acid was stated to give "a copious light-blue precipitate with the ferridcyanide of potassium, and a still more abundant one of a deeper colour with the ferrocyanide of potassium." The volumetric test required the presence in the compound of such an amount of ferrous salt as would correspond to at least 1.428 per cent. Fe, or 3.791 per cent. $\text{Fe}_3(\text{AsO}_4)_2$.

In the Pharmacopœia of 1867 the definition of the compound and the method for its preparation were practically the same as in the previous edition. An important change was made, however, in the description of its character, since it was stated that its solution in hydrochloric acid "gives a copious light-blue precipitate with the yellow prussiate of potash, and a still more abundant one of a deeper colour with the red prussiate of potash." This indication of a predominating amount of ferrous salt in the compound likewise found expression in the quantitative test, which stated that it should require such an amount of volumetric solution of potassium

bichromate for its oxidation as would correspond to at least 14.28 per cent. Fe, or 37.91 per cent. $\text{Fe}_3(\text{AsO}_4)_2$. As these figures are exactly ten times as great as those in the edition of 1864, one might attribute them to a typographical error were it not for the fact that in both cases they are obviously quite incorrect.³

In the Pharmacopœia of 1885 *Ferri Arsenias* was defined as "arseniates of iron, with some oxide." In this edition the proportions of the salts directed to be used in its manufacture differed considerably from those of the earlier pharmacopœias, and were as follows: Ferrous sulphate ($20\frac{3}{4}$ parts), sodium arsenate, dried at 300° F. ($15\frac{3}{4}$ parts), and sodium bicarbonate ($4\frac{1}{2}$ parts); the latter salt having been adopted for the neutralisation of the sulphuric acid produced by the reaction, in place of the sodium acetate previously employed. It will be seen from the above proportions that the amount of sodium arsenate, relative to that of ferrous sulphate employed, is nearly 75 per cent. greater than in the two preceding editions. The qualitative test remained the same as in the Pharmacopœia of 1867, indicating a predominance of ferrous salt, but a very great change was again made in the quantitative test, which required that the preparation should contain such an amount of ferrous salt as would correspond to at least 3.78 per cent. Fe, or 10.03 per cent. $\text{Fe}_3(\text{AsO}_4)_2$.

In the Pharmacopœia of 1898, which is the present official standard, a slight change was made in the definition of iron arsenate, as noted in the beginning of this paper. An alteration was also made in the wording of the qualitative test, which now reads as follows: "It affords the reactions characteristic of ferrous and ferric salts and of arsenates." The quantitative test requires the preparation to contain an amount of ferrous salt "corresponding to nearly $12\frac{1}{2}$ per cent. of hydrous, or 10 per cent. of anhydrous, ferrous arsenate." The exact figures, as calculated from the stated amount of volumetric solution of potassium bichromate of the B.P. (1 C.c. = 0.00556 Fe), would be represented by 3.72 per cent. Fe, 9.89 per cent. $\text{Fe}_3(\text{AsO}_4)_2$, or 12.28 per cent. $\text{Fe}_3(\text{AsO}_4)_2, 6\text{H}_2\text{O}$, and are thus in practical

³ W. H. Symons (*Pharm. Journ.*, January 19, 1884, p. 562) has recorded that two samples of iron arsenate, examined by him, were found to contain 6.5 and 5.47 per cent. respectively of ferrous salt, whereas a preparation made by himself, according to the directions of the Pharmacopœia, contained 27.2 per cent. of ferrous arsenate. The latter figure, although considerably below the pharmacopœial requirement of the time, is still so high as to indicate some error in the determination. Compare also Nicholls (*'Year-Book of Pharmacy,'* 1903, p. 576.)

agreement with the requirement of the Pharmacopœia of 1885.

Preparations known as iron arsenate have also been recognised by the Pharmacopœias of France, Italy, Spain, and Mexico⁴, but the proportions of the salts directed to be employed in their manufacture differ materially in all of them, and, as might be expected, the resulting products differ appreciably in their composition.

The French Pharmacopœia, edition of 1895, under the title of *Arséniate Ferreux*, recognises a compound to which the formula FeHAsO_4 is assigned, and which is directed to be prepared by mixing a solution of 50 grammes of crystallised sodium arsenate with a solution of 10 grammes of crystallised ferrous sulphate. The resulting precipitate is of such a character that it cannot be washed either by decantation or on a filter, and can only be collected by forcible expression on a strainer. If the mixture be allowed to stand for a few hours, the precipitate becomes to a large extent redissolved. Only qualitative tests are given for the identity and purity of the product.

The Italian Pharmacopœia of 1892, under the title of *Arseniato Ferroso-Ferrico*, recognises a compound which is directed to be prepared by adding a solution of seven parts of crystallised sodium arsenate ($\text{Na}_2\text{HAsO}_4, 8\text{H}_2\text{O}$) to a solution of six parts of crystallised ferrous sulphate, washing the resulting precipitate, and drying it at a temperature not exceeding 30°C . In addition to some tests for the identity and purity of the product, it is stated that 100 parts of it correspond to about 46 parts of arsenic acid, H_3AsO_4 . Among the various pharmacopœias which recognise iron arsenate, the Italian is the only one which prescribes any control respecting its arsenical content.

The Spanish Pharmacopœia, seventh edition (1905), under the title of *Arseniato de Hierro*, recognises a compound which is stated to be a ferroso-ferric arsenate. It is directed to be prepared by adding to a solution of 100 parts of crystallised ferrous sulphate a solution of 275 parts of crystallised sodium arsenate, until, after stirring and allowing the precipitate to subside, the clear supernatant liquid

⁴ The statements in the 'U.S. Dispensatory,' eighteenth edition, p. 605, that "This is an official salt of the British Pharmacopœia, which as yet is the only one that has adopted it," and in the 'National Standard Dispensatory,' p. 617, that, besides the British and French, "no other pharmacopœias recognise ferrous arsenate," are obviously not quite correct.

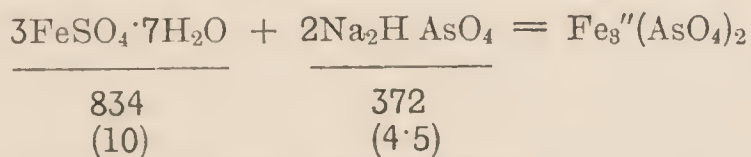
has an alkaline reaction.⁵ No specific tests are given for the presence of either iron or arsenic in the compound, nor is any requirement made respecting the amount which it should contain of these elements.

The Mexican Pharmacopœia, second edition (1884), has adopted both an arsenite and an arsenate of iron, the latter bearing the official title of *Arseniato de Fierro*. This is directed to be prepared by mixing a solution of 24 parts of crystallised ferrous sulphate with a solution of 20 parts of potassium arsenate, KH_2AsO_4 . No requirement is made respecting the amount of iron or arsenic to be contained in the product.

The variation in the proportions of the salts directed by the previously mentioned pharmacopœias to be employed in the preparation of iron arsenate may be seen by the following table. For convenience of comparison the prescribed amounts of alkali arsenate are calculated into the corresponding amounts of anhydrous sodium arsenate, and uniformly with reference to 10 parts of crystallised ferrous sulphate.

—	$\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$	Na_2HAsO_4 .
British Pharmacopœia (1898)	10 parts	7·6 parts
French Pharmacopœia (1895)	10 "	29·8 "
Italian Pharmacopœia (1892)	10 "	6 6·6 "
Spanish Pharmacopœia (1905)	10 "	16·4 "
Mexican Pharmacopœia (1884)	10 "	7 8·6 "

The calculated amount of anhydrous sodium arsenate which would be required to react with ten parts of crystallised ferrous sulphate, for the production of a normal ferrous arsenate, is 4·5 parts, in accordance with the following essential factors of the equation :—

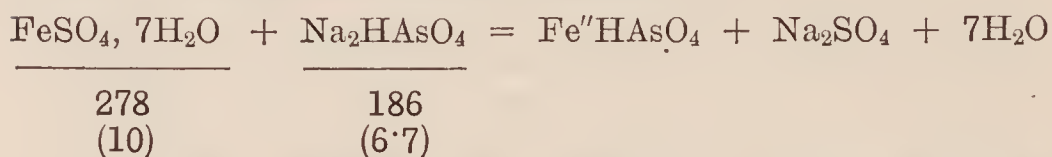


⁵ We have observed that two-thirds of the prescribed amount of sodium arsenate is sufficient to impart to the liquid an alkaline reaction, but it has not been found practicable to wash the precipitate by decantation as directed.

⁶ The Italian Pharmacopœia considers the official sodium arsenate to contain eight molecules of water, whereas the other pharmacopœias state seven molecules.

⁷ 8·6 Gm. of disodium hydrogen arsenate is the equivalent in arsenic content of 8·33 Gms. of potassium dihydrogen arsenate, the salt which the Mexican Pharmacopœia directs to be employed.

For the formation of a salt of the composition $\text{Fe}''\text{HAsO}_4$, which is that assigned to the compound of the French Pharmacopœia, 10 parts of crystallised ferrous sulphate would require, theoretically, 6·7 parts of anhydrous sodium arsenate, in accordance with the equation :—



In order to ascertain the composition of the compounds which are officially recognised as iron arsenate, small quantities were prepared, as nearly as possible in accordance with the directions of the respective pharmacopœias, with the exception of the Mexican, dried uniformly at a temperature not exceeding 38°C ., and submitted to analysis. In addition to these preparations, two representative samples of the B.P. product, as supplied by English manufacturers, were examined. The method of analysis employed was as follows :—

(1) *Estimation of the Ferrous Iron*.—About 1 gramme of the salt, accurately weighed, was dissolved with the aid of a gentle heat in 20 per cent. sulphuric acid, in a flask provided with a Bunsen valve. After the salt had completely dissolved, the liquid was allowed to cool, then diluted with a little water, and titrated with a standard solution of potassium permanganate.

(2) *Estimation of the Total Iron and the Arsenic*.—About 0·5 gramme of the salt, accurately weighed, was dissolved in 20 C.c. of 15 per cent. hydrochloric acid, and the liquid diluted with water to the measure of 100 C.c. It was then saturated with sulphur dioxide, in order to reduce the arsenic acid to the arsenous state. After removing the excess of sulphur dioxide by a gentle heat, the liquid, while still warm, was treated with hydrogen sulphide until the arsenic was completely precipitated. The arsenous sulphide was collected on a filter, washed with water containing a little hydrogen sulphide, and the filtrate and washings reserved for the determination of the iron. After drying the arsenous sulphide, it was transferred as completely as possible to a flask, and oxidised with fuming nitric acid. The small amount of sulphide adhering to the filter was removed by a little strong solution of ammonia, the alkaline liquid evaporated to dryness, and this arsenical residue likewise oxidised with nitric acid, after which it was added to the main portion in the

flask. The entire arsenical liquid was then evaporated, a little dilute sulphuric acid being added toward the end of the operation to facilitate the complete elimination of the nitric acid, and the arsenic acid thus obtained converted into ammonio-magnesium arsenate in the usual manner. The latter compound, after drying at 100-105° C., was weighed as $\text{Mg}(\text{NH}_4)\text{AsO}_4, \frac{1}{2}\text{H}_2\text{O}$, and from this the percentage of arsenic calculated.

The filtrate and washings from the original precipitate of arsenous sulphide were concentrated, a little nitric acid added to completely oxidise the iron, the latter then precipitated by ammonia, and the precipitate, after being washed, dried, and ignited, weighed as ferric oxide, Fe_2O_3 .

For convenience of comparison the results afforded by these analyses may be tabulated as follows⁸ :—

Designation of Preparation.	Ferrous Iron. Per Cent.	Total Iron. Per Cent.	Arsenic (As.) Per Cent.
British Pharmacopœia (1898)	7.11	21.15	28.58
French Pharmacopœia (1895)	4.45	20.87	28.15
Italian Pharmacopœia (1892)	9.10	24.65	28.09
Spanish Pharmacopœia (1905)	6.38	22.14	29.70
Commercial Specimen	4.62	26.31	30.67
„ „	4.48	27.19	29.76

The amount of ferrous iron contained in the specimen of iron arsenate prepared in accordance with the directions of the British Pharmacopœia—namely, 7.11 per cent., would correspond to 18.9 per cent. of anhydrous ferrous arsenate. The pharmacopœial test requires an amount of ferrous iron which shall correspond to, at least, nearly 10 per cent. of anhydrous ferrous arsenate. On the other hand, 18.9 per cent. of ferrous arsenate would correspond to 6.36 per cent. of arsenic (As), whereas the total percentage of arsenic in the respective specimen was 28.58 per cent., thus showing that even a freshly prepared iron arsenate consists to a large extent of a ferric salt. Furthermore, a comparison of the relative percentages of ferrous iron and arsenic found in the preparations enumerated in the above table, also clearly

⁸ A number of analyses of official iron arsenate have been recorded by Nicholls, which show a high degree of variation in its composition. The method employed by him for the determination of the arsenic was different from that above described, but he gives no details respecting the determination of the iron (*Pharm. Journ.*, 1903, 71, p. 164; 'Year-Book of Pharmacy,' 1903, p. 576).

demonstrates that the official test permits of no deduction whatever respecting the proportion of arsenic which such a preparation may contain.

As previously noted, the only official standard for the arsenic content of iron arsenate is that of the Italian Pharmacopœia, which requires about 46 per cent. H_3AsO_4 , corresponding to 24·29 per cent. As.

THE WELLCOME CHEMICAL RESEARCH LABORATORIES.
